Reductive Alkylations of Dimethylamine Using Titanium(IV) Isopropoxide and Sodium Borohydride: An Efficient, Safe, and Convenient Method for the Synthesis of *N,N*-Dimethylated Tertiary Amines

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The development of safe and efficient methods for the synthesis of amines remains an important theme in chemical research because of their versatile utility[1] as intermediates for drugs and agrochemicals. The *N,N*-dimethylalkylamines are particularly useful as ligands[2] in homogeneous catalytic asymmetric transformations, as a modifier[3] for reversed phase chromatography, and as a buffer[4] in sequential analysis of proteins and peptides, among other applications.[5]

Methods described[6,7] for the synthesis of *N,N*-dimethylated tertiary amines via alkylation of dimethylamine often involve a large excess of the gaseous dimethylamine and elevated temperatures and pressures. Nevertheless, most of these procedures suffer from limitations. In particular, yields are often low, quaternary salt formation is common, and secondary alkylating agents cannot be used due to the preponderant elimination reactions. Moreover, many of these methods are described in the patent[7] literature.

The most direct approach for the preparation of amines is the reductive amination[8] of an appropriate aldehyde or ketone. Among the hydride reagents, sodium cyanoborohydride[8b] (Borch reduction) has been widely used to effect this transformation in recent years. However, the use of expensive and highly toxic sodium cyanoborohydride that risks the presence of residual cyanide in the product and workup system makes this procedure less attractive to industry. In the context of our interest in the development of a mild and environmentally benign reagent system for reductive amination reactions, we have recently reported[9] on an efficient method for the reductive aminations of formaldehyde using the combination of titanium(IV) isopropoxide and sodium borohydride. In a complementary study, this paper presents results for the application of this reagent system in the reductive alkylations of dimethylamine with a variety of aldehydes and ketones at room temperature, an effective and very simple method for the preparation of *N,N*-dimethylalkylamines of high purity in good to excellent yields. A mixture of dimethylamine hydrochloride and triethylamine has been employed as the convenient source of nucleophilic dimethylamine; this requires no special handling techniques and obviates the use of excess gaseous amine. The reaction is possibly proceeding through the formation of (dimethylamino)carbinolatotitanium(IV) complex 1 (Scheme 1) as an intermediate[10] which is reduced either directly or via transient iminium species. Titanium(IV) isopropoxide has been utilized[9,11] as a mild reagent compatible with a vareity of potentially acid-sensitive functional groups such as acetals, lactams, acetonide, and *tert*-butyldimethylsilyl ethers.

The method is general for a variety of aldehydes and ketones containing potentially acid-sensitive functional groups. The molar ratio of the reactants and the results

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Scheme 1

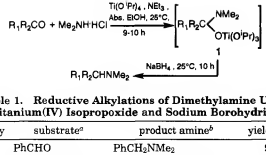

Table 1. Reductive Alkylations of Dimethylamine Using Titanium(IV) Isopropoxide and Sodium Borohydride

entry	substrate[a]	product amine[b]	yield[c] (%)
1	PhCHO	$PhCH_2NMe_2$	95
2	*p*-ClC_6H_4CHO	*p*-$ClC_6H_4CH_2NMe_2$	96
3	*p*-$AcHNC_6H_4CHO$	*p*-$AcHNC_6H_4CH_2NMe_2$	96
4	*p*-NCC_6H_4CHO	*p*-$NCC_6H_4CH_2NMe_2$	95
5	*m*-$MeOC_6H_4CHO$	*m*-$MeOC_6H_4CH_2NMe_2$	95
6	*m*-$O_2NC_6H_4CHO$	*m*-$O_2NC_6H_4CH_2NMe_2$	95
7	$PhCH_2CHO$	$PhCH_2CH_2NMe_2$	90
8	$PhCH_2CH_2CHO$	$PhCH_2CH_2CH_2NMe_2$	90
9	$Me(CH_2)_6CHO$	$Me(CH_2)_6NMe_2$	88
10	$PhCH_2CH_2COMe$	$PhCH_2CH_2CH(Me)NMe_2$	75
11	*m*-$MeOC_6H_4COMe$	*m*-$MeOC_6H_4CH(Me)NMe_2$	72
12			75
13			75
14			77
15			75

[a] The commercially available starting aldehydes and ketones were distilled or recrystallized from appropriate solvent mixtures; the ratio of carbonyl compound:dimethylamine hydrochloride: triethylamine:titanium(IV) isopropoxide:sodium borohydride is 1:2:2:2:1.5. [b] Spectroscopic and physical constant data for all compounds were in complete agreement with the literature data or authentic samples. [c] Yields are of isolated and purified products.

obtained for a representative group of carbonyl compounds are collated in Table 1.

As shown in Table 1, aldehydes reacted faster than the ketones and pure products were isolated by simple dichloromethane extraction. The ketones are reductively aminated in good yields; the crude *N,N*-dimethylamines were purified by simple extraction with hydrochloric acid (2 N). It is noteworthy that, in contrast to the existing acid-mediated reductive amination protocols, the present method is equally applicable to enolizable carbonyl compounds. The reaction conditions were found to be tolerant to a number of groups such as chloro, methoxy, cyano, nitro, amido, and urethane. The neutral nonaqueous reaction conditions, the simple workup, the isolation of pure products without chromatograhic separations, the high yields, and the use of safe and cheap reagents with no special handling techniques are the notable advantages of the present method. Moreover, because of the compatibility of titanium(IV) isopropoxide with a variety of acid-sensitive functional groups including acetonide, *tert*-butyldimethylsilyl ether, and acetals, this method can provide an easy access to analogous tertiary amines bearing functionalized pendant chains.

In conclusion, a general, preparatively efficient, simple method for the preparation of *N,N*-dimethylalkylamines is identified via reductive alkylation of dimethylamine using titanium(IV) isopropoxide and sodium borohydride. A mixture of dimethylamine hydrochloride and triethylamine is utilized as the convenient source of nucleophilic dimethylamine. Because of the safe and cheap reagents with no special handling techniques, the simple workup, the high yields of pure products, and the compatibility of this one-pot procedure with a number of normally reducible and acid-sensitive functional groups, this method should find wide application. Further studies addressing the possibility of asymmetric induction in the reductive aminations of unsymmetrical ketones using chirally modified titanium(IV) isopropoxide as well as application of this methodology in the synthesis of primary and secondary amines are currently underway.

Experimental Section

General Procedure for the Reductive Alkylations of Dimethylamine. To a solution of triethylamine (2.0 g, 20 mmol) in absolute ethanol (15 mL) were added dimethylamine hydrochloride (1.65 g, 20 mmol), titanium(IV) isopropoxide (5.7 g, 20 mmol), and the starting aldehyde (10 mmol). The reaction mixture was stirred at 25 °C for 9–10 h, after which sodium borohydride (0.57 g, 15 mmol) was added and the resulting mixture was further stirred for a period of 10 h at 25 °C. The reaction was then quenched by pouring the mixture into aqueous ammonia (30 mL, 2 N), the resulting inorganic precipitate was filtered and washed with dichloromethane (50 mL), and the aqueous filtrate was extracted with dichloromethane (50 mL × 2). The combined dichloromethane extracts were dried (K_2CO_3) and concentrated in vacuo to give pure *N,N*-dimethylated tertiary amines.

For the reductive aminations of ketones, the same general procedure was used except that the combined dichloromethane extracts were next extracted with hydrochloric acid (10 mL × 2, 2 N) to seperate the neutral materials. The acidic aqueous solution was made alkaline (pH = 10) by slow addition of (10%, w/v) aqueous NaOH and extracted with dichloromethane (50 mL × 2). The combined organic extracts were dried (K_2CO_3) and concentrated in vacuo to give pure *N,N*-dimethylated alkylamines.

Supporting Information Available: ^{1}H NMR spectra of entries 1–6, 8, 10, 11, 14, and 15 (11 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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